

Clinical profiles and prognosis of acute heart failure in adult patients with dystrophinopathies on home mechanical ventilation

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Abstract

Aims Duchenne muscular dystrophy (DMD) is characterized by respiratory and heart involvements. In the context of permanently wheelchair bound and on mechanical ventilation (MV) patients, the clinical presentation of acute heart failure (AHF) syndrome may be atypical. We sought to describe clinical and genetic profiles and to determine prognosis of DMD and Becker muscular dystrophy (BMD) patients on home MV (HMV), hospitalized for AHF.

Methods and results We included genetically proven DMD and BMD patients on HMV admitted for AHF. A total of 13 patients (11 DMD and 2 BMD) fulfilled the inclusion criteria. Median age was 34.0 [interquartile range (IQR) 26.0; 40.0] years. Median pulmonary vital capacity was 9.0% (6.0; 15.0) of predicted value. Long-term invasive ventilation was performed in 69% of patients. All the 11 DMD patients carried out-of-frame *DMD* gene mutations. At admission, dyspnoea was present in 46%, lipothymia in 23%, and abdominal discomfort in 38.4% of patients. A total of 53.8% of patients showed anasarca. Cardiogenic shock presentation was found in six patients (46%). Ejection fraction was severely altered [median 25% (IQR 20; 30)]. Intra-hospital mortality rate was 30%, reaching 53.8% after 1 year. Previous episodes of AHF ≥ 2 were associated with intra-hospital mortality ($P = 0.025$). In patients with cardiogenic shock, intra-hospital mortality rate was 66.6%, reaching 83.3% after 1 year.

Conclusions In adult DMD and BMD patients with severe ejection fraction alteration and on HMV, admitted for AHF, right cardiac signs are frequent. The intra-hospital and 1 year mortality rate was high and was associated with previous episodes of AHF ≥ 2 .

Keywords Dystrophin; N-terminal domain; Rod domain; Duchenne muscular dystrophy; Becker muscular dystrophy; Heart failure

Received: 3 November 2016; Revised: 8 February 2017; Accepted: 24 March 2017

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Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive genetic disorder, caused by mutations in the *DMD* gene and affects 1 of 3500 male births.¹ The *DMD* gene is the largest gene known in humans (2.3Mb of genomic DNA). Depending on the presence or the absence of the translational reading frame, mutations in the *DMD* gene lead to DMD in case of out frame mutations. Conversely, the milder form, Becker

muscular dystrophy (BMD), results from in-frame *DMD* mutations.^{2–4} In DMD, the underlying gene mutations cause the absence of dystrophin, a protein located on the inner side of the skeletal and the cardiac muscle cells, linking the internal cytoskeleton to the extracellular matrix.⁵ Beside the functional limitation due to the involvement of the skeletal muscles, respiratory and cardiac muscles involvements in DMD patients had the main impact on the life expectancy. Over the last few decades, the possibility to support the pulmonary function

with mechanical ventilation has radically improved the survival of DMD patients.^{6,7} In the meantime, the support of this vital function has allowed the clinical emergence of advanced cases of heart failure. In this context of severely affected patients, usually wheelchair bound and on mechanical ventilation, the clinical presentation of acute heart failure (AHF) syndrome may be atypical and the assessment of its severity a difficult task. Some of these patients are admitted to Intensive Care Unit (ICU), but clinical pictures and outcomes of such patients are poorly reported. In this study, we sought (i) to describe clinical profiles and genetic pattern and (ii) to determine intra-hospital mortality rate and 1 year mortality rate of patients with DMD and BMD on home mechanical ventilation (HMV), hospitalized in ICU for AHF.

Materials and methods

Study setting

The ICU of the Raymond Poincaré University Hospital is a reference centre that specializes in respiratory and cardiac management of neuromuscular disorders at advanced stages. In this unit, neuromuscular patients are followed on annual basis in a multidisciplinary consultation that includes cardiac and pulmonary assessment in the home ventilation unit because of restrictive respiratory failure.

Study design

Since 2006–16, a total of 137 admissions of patients suffering from dystrophinopathies (DMD and BMD) were notified into this unit. For the present study, we included genetically proven DMD and BMD patients on HMV because of significant chronic respiratory insufficiency and with chronic cardiomyopathy and admitted in the ICU of the Raymond Poincaré University Hospital for AHF.

We retrospectively reviewed the medical records of these patients and collected clinical setting, electrocardiogram data, left ventricular ejection fraction (EF) from echocardiography, B-type natriuretic peptide, and blood creatinine level from blood results at admission, intra-hospital mortality, and mortality within 1 year. Doppler echocardiographies were performed by the same experienced cardiologist (A.F.) with a Siemens CV70 device (ACUSON), according to the guidelines issued by the American Society of Echocardiography. Spirometry variables and lung volumes were routinely measured using a Vmax 229 SensorMedics System (Yorba Linda, CA, USA) according to standard guidelines.

The study was performed in compliance with the ethical principles formulated in the declaration of Helsinki and was approved by the French regulatory board (*Commission*

Nationale de l'Informatique et des Libertés). The study was registered in ClinicalTrials.gov (identifier: NCT02685215).

Clinical definitions

AHF is defined as a gradual or rapid change in heart failure signs and symptoms requiring urgent therapy.⁸ Cardiogenic shock is a life-threatening emergency and is defined by persistent hypotension and tissue hypoperfusion due to cardiac dysfunction in the presence of adequate intravascular volume and left ventricular filling pressure.

Genetic analysis

Semi-quantitative fluorescent multiplex PCR using genomic DNA was performed for detecting deletions and duplications.⁹ Other types of mutations were detected by sequencing all *DMD* gene exons or by the analysis of muscle dystrophin mRNA (reverse transcription (RT)–PCR).⁹ For each patient, we recorded the mutation type and the involved gene exons. The dystrophin protein contains several functional domains, including the N-terminal, the rod domain, the cysteine-rich domain, and the C-terminal. The rod domain is composed of three subdomains separated by four hinges (H1, H2, H3, and H4), subdomains that we respectively indicated as <H2, H2–H3, and >H3 in *Table 1*. For each patient, we determined the most distal dystrophin domain theoretically involved by the *DMD* gene mutation and beyond that which the protein is truncated if any dystrophin is produced. Therefore, the more distal is the mutation, less are the affected domains if any residual dystrophin is synthesized. For instance, out-of-frame mutations involving the N-terminal affect theoretically all the dystrophin domains while out-of-frame mutations involving the C-terminal spare the N-terminal and the entire rod domain.

Statistics

Continuous variables were described by median \pm interquartile range (IQR) and compared by Wilcoxon test; dichotomous or categorical variables were described by number of subjects and percentage and compared by Fisher's exact test. Statistical analysis was performed using R® (<http://www.R-project.org/>).

Results

Study population (*Table 1*)

Among the 137 admitted patients, 13 (11 DMD and 2 BMD) fulfilled the inclusion criteria of our study. Median age was

Table 1 Genetic, clinical profiles, and mortality of patients with Duchenne muscular dystrophy

Patient no./phenotype/age (years)	Patient's characteristics		Cardiac history		AHF characteristics						
	DMD gene mutation	More distally involved dystrophin domain	VC (%) invasive or non-invasive HMV/HMV duration	Previous AHF episodes: yes or no (number)	EF (%) EKG	Cardiac drugs	Clinical presentation of AHF	BNP (pg/mL)	Great (μmol/L)	AHF drug management	Outcome
1/DMD/26	c.141dup, p.Arg48GlufsX41	N-terminal	8//24/24 h	Yes (n = 3)	15/RBBB	ACEI, BB, D, MRA, digoxin	AD, lipothymia, ascites, BP 60/30, pleural effusion	—	33	Inotropes	IH death
2/DMD/23	Del exon 46–52	Rod domain [H2–H3]	22/NI/10/24 h	Yes (n = 1)	29/LBBB	ACEI, BB, D	Dyspnoea, BP 90/40	1199	<20	MT	Death < 1 y
3/DMD/31	c.4231C > T, p.Gln1411X	Rod domain [H2–H3]	10//24/24 h	Yes (n = 4)	20/LBBB	ACEI, BB, D	Dyspnoea, BP 70/30, sepsis	>5000	<20	Inotropes, vasopressors	IH death
4/DMD/38	Dup exon 3–7	N-terminal	15//24/24 h	Yes (n = 1)	15/RBBB	ACEI, BB, D	Leg oedema, anasarca, BP 120/80	334	<20	MT	Death < 1 y
5/DMD/38	c.5602_5605delAGA, p.Arg1868GlufsX5	Rod domain [H2–H3]	6//24/24 h	Yes (n = 1)	20/LBBB	ACEI, BB, D, MRA	Leg oedema, anasarca, SBP 77/42, pulmonary congestion	—	31	MT	Survival
6/DMD/34	Del exon 50–52	Rod domain [H2–H3]	5//24/24 h	Yes (n = 1)	30/LBBB	ACEI, BB, D	Leg oedema, AD, ascites, BP 90/60	—	—	MT, CRT	Survival
7/DMD/26	Del exon 8–13	N-terminal	12//24/24 h	Yes (n = 1)	20/Normal	ACEI, BB	AD, leg oedema, ascites, BP 70/30, pleural effusion	—	—	Inotropes	Death < 1 y
8/DMD/20	Del exon 52–79	Rod domain [>H3]	32/NI/10/24 h	No	20/LBBB	ACEI, BB, D	Dyspnoea, BP 80/40,	2370	36	MT	IH death
9/DMD/27	Dup exon 44–49	Rod domain [H2–H3]	9//24/24 h	Yes (n = 1)	45/RBBB	ACEI, BB	pleural effusion, Leg oedema, BP 95/45, sepsis	466	30	MT, dialysis	Survival
10/DMD/40	Del exon 8–9	N-terminal	6/NI/10/24 h	No	35/RBBB	ACEI, BB, D	Dyspnoea, sepsis, BP 116/92	—	—	MT	Survival
11/BMD/49	Dup exon 14–47	Rod domain [<H2]	5//24/24 h	Yes (2)	30/LBBB	ACEI, BB, D	Leg oedema, ascite, anasarca, pleural effusion, BP 75/50	362	42	Inotropes, vasopressors, dialysis	IH death
12/BMD/49	c.94 – 1G > T	N-terminal	23/NI/8/24 h	No	25/LBBB	ACEI, BB, D	Dyspnoea, BP 120/80	—	—	MT, CRT-D	Survival
13/DMD/45	Del exon 45–50	Rod domain [H2–H3]	1//24/24 h	No	30/LBBB	ACEI	Lipothymia, Dyspnoea, BP 80/49	(Nt-pro BNP 12000)	33	Inotropes	Survival

ACEI, angiotensin-converting enzyme inhibitor; AD, abdominal discomfort; BB, beta-blocker; BNP, B-type natriuretic peptide; BP, blood pressure in mmHg; Creat, creatinine level in blood; CRT-D, cardiac resynchronization therapy + defibrillator; D, loop diuretic; De, deletion; Dup, duplication; EF, left ventricular ejection fraction (%); HMV, home mechanical ventilation; I, invasive ventilation; IH, intra-hospital; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist; MT, medical therapy; MV, mechanical ventilation; N, normal; NI, non-invasive ventilation; RBBB, right bundle branch block; y, years.

34.0 (IQR 26.0; 40.0) years. At baseline, all patients were wheelchair bound and disclosed chronic restrictive respiratory failure needing HMV. The two BMD patients (nos. 11 and 12) respectively lost ambulation at 23 and 19 years old, thus falling into the severe BMD spectrum. Gastrostomy was present in four patients out of 13 (30.7%). Median pulmonary vital capacity was 9.0% (6.0; 15.0) of predicted value. Long-term invasive ventilation was performed in nine of 13 patients (69%). Eleven patients were already treated with angiotensin-converting enzyme inhibitors (ACEI), 11 with beta-blockers and 10 with diuretics. Eight patients had previous hospitalizations for AHF; among them, three patients had ≥ 2 episodes of previous hospitalization for AHF. Two patients had an elevation of liver transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2 -fold the upper limit of the normal range), and six patients showed a >2 -fold elevation of the gamma-glutamyl transpeptidase.

Genetic results

Genetic results regarding the 13 patients are shown in *Table 1*. Mutations in the *DMD* gene were identified in all the 13 patients. The two BMD patients (nos. 11 and 12) carried respectively an in-frame large duplication of exons 14–47 and intron 2 acceptor splice site mutation (c.94 – 1G > T) that probably lead to in-frame exon skipping. Unfortunately, no muscle biopsy was available for mRNA analysis in this latter patient. However, muscle mRNA analysis in another patient carrying the same intronic mutation clearly showed exon 3 skipping at the mRNA level making this skipping likely in patient 12. In all the 11 remaining DMD patients, we identified out-of-frame mutations including large exonic deletions (six patients) and duplications (three patients), one nucleotide insertion in exon 3 (one patient), four nucleotides deletion in

exon 40 (one patient), and a premature stop codon in exon 30 (one patient). The exons 52–79 deletion found in patient 8 encompassed the *DMD* gene and involved contiguous genes (at least *NROB1* and *GK* genes) resulting in mental retardation, congenital adrenal hypoplasia, and glycerol kinase deficiency. Five of these mutations involved all the dystrophin domains from the N-terminal domain (patients 1, 4, 7, 10, and 12), one spared the N-terminal domain (patient 11), six spared the N-terminal and <H2 domains (patients 2, 3, 5, 6, 9, and 13), and one spared the N-terminal and <H2 and H2–H3 domains (patient 8).

Clinical presentation of AHF at admission

Regarding symptoms at admission, dyspnoea was present in six patients (46%), lipothymia in three patients (23%), and abdominal discomfort in five patients (38.4%) (*Figure 1*).

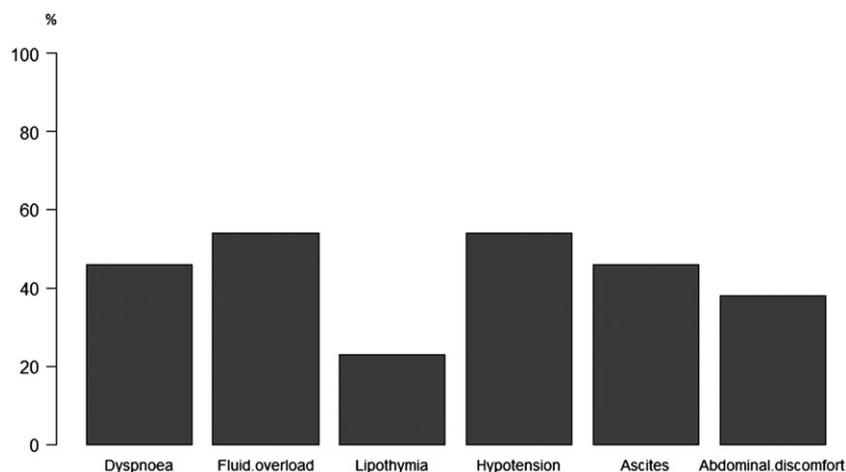
Among clinical signs, hypotension with systolic blood pressure <80 mmHg was present in seven patients. Fluid overload signs were frequent as six patients (46%) presented ascites and leg oedema, and seven patients (53.8%) showed anasarca. Cardiogenic shock presentation was found in six patients (46%) and was associated with anasarca in four patients. Complete left bundle branch block (LBBB) was present in eight patients (61%).

On echocardiography, EF was severely altered [median 25% (IQR 20; 30)]. Median B-type natriuretic peptide level was 1199.0 (414.0; 3685.0) pg/mL, and a blood creatinine level >20 $\mu\text{mol/L}$ was found in six patients.

Intra-hospital and 1 year mortality

Intra-hospital mortality rate in patients admitted for AHF was 30% in the study population (4/13 patients). One-year

Figure 1 Distribution of symptoms and clinical signs at admission



mortality rate, after hospitalization for AHF, was high, reaching 53.8% (7/13 patients). Mortality rate was notably high in patients with previous admission for AHF. In patients with cardiogenic shock, intra-hospital mortality rate was 66.6%, reaching 83.3% after 1 year.

Clinical and genetic parameters associated 1 year mortality

Along patients that died during the year after hospitalization for AHF, 42.9% disclosed mutations that theoretically affect all the dystrophin domains (i.e. N-terminal) while 40% showed mutations that theoretically involve one or several parts of the rod domain without reaching the significance threshold. However, the fact that there was no patient with AHF carrying the mutations sparing the N-terminal and rod domains (i.e. those affecting only C-terminal) may suggest that involvement of the N-terminal, and the rod domains is more deleterious for the cardiac function than the involvement of the C-terminal. The presence of ≥ 2 previous episodes of AHF was associated with intra-hospital mortality ($P = 0.025$). Tables 2 and 3 summarize clinical and genetic factors associated with intra-hospital and 1 year mortality.

Discussion

Cardiomyopathy is a classical complication in patients with DMD and affects the prognosis of these patients. In the

Table 2 Genetic and clinical factors associated with intra-hospital mortality

	Intra-hospital non-survivors (n = 4)	Intra-hospital survivors (n = 9)	P
Age (years)	28.5 [24.5; 35.5]	38.0 [27.0; 40.0]	0.486
VC (% predicted)	12 [7; 19]	9 [6; 15]	0.698
Previous episodes	3 (75.0)	0 (0.0)	0.025
AHF ≥ 2 (n, %)			
Rod domain (n, %)	2 (50.0)	5 (55.6)	1.00
N-terminal domain (n, %)	1 (25.0)	4 (44.4)	0.962
Ascites + leg oedema (n, %)	2 (50.0)	4 (44.4)	1.00
Dyspnoea (n, %)	3 (75.0)	3 (33.3)	0.431
SBP < 80 mmHg (n, %)	4 (100.0)	3 (33.3)	0.105
Creatinine > 20 $\mu\text{mol/L}$ (n, %)	3 (75.0)	3 (33.3)	0.895
Liver enzymes > 2 ULN (n, %)	2 (50.0)	4 (44.4)	1.00
LBBB (n, %)	3 (75.0)	5 (55.6)	0.962
EF (%)	20 [19; 22]	29 [20; 30]	0.270

AHF, acute heart failure; EF, left ventricular ejection fraction (%); LBBB, left bundle branch block; SBP, systolic blood pressure; VC, vital capacity. Liver enzymes > 2 ULN: AST, aspartate aminotransferase; ALT, alanine aminotransferase; and/or GGT, gamma glutamyl transferase; elevated more than two-fold the upper limit of the normal range (ULN).

Table 3 Genetic and clinical factors associated with 1 year mortality

	1 year non-survivors (n = 7)	1 year survivors (n = 5)	P
Age (years)	26.0 [24.5; 34.5]	38.0 [34.0; 40.0]	0.142
VC (% predicted)	15 [10; 18]	6 [6; 9]	0.289
Previous episodes	3 (42.9)	0 (0.0)	0.310
AHF ≥ 2 (n, %)			
Ascites + leg oedema (n, %)	4 (57.1)	2 (40.0)	1.00
Dyspnoea (n, %)	4 (57.1)	2 (40.0)	1.00
SBP < 80 mmHg (n, %)	6 (85.7)	1 (20.0)	0.092
Creatinine > 20 $\mu\text{mol/L}$ (n, %)	3 (42.9)	2 (40.0)	1.00
Liver enzymes > 2 ULN (n, %)	3 (42.9)	3 (60.0)	1.00
Rod domain (n, %)	3 (42.9)	3 (60.0)	1.00
N-terminal domain (n, %)	3 (42.9)	2 (40.0)	1.00
LBBB (n, %)	4 (57.1)	3 (60.0)	1.00
EF (%)	20 [18; 24]	30 [25; 35]	0.068

AHF, acute heart failure; EF, left ventricular ejection fraction (%); LBBB, left bundle branch block; SBP, systolic blood pressure; VC, vital capacity.

Liver enzymes > 2 ULN: AST, ALT, and/or GGT elevated more than two-fold the upper limit of the normal range (ULN).

general cardiologic population, heart failure exacerbation is classically associated with volume overload and/or low cardiac output. The clinical presentation of AHF in patients with DMD may be atypical¹⁰ for several reasons: patients with advanced DMD have an extensively reduced possibility of perform any effort, being wheelchair-bound, and may thus not present effort-related symptoms. Furthermore, respiratory symptoms like dyspnoea may be hampered, because their respiration is supported mechanically because of the disease-related restrictive respiratory failure, and mechanical ventilation protect against high left ventricular filling.¹¹ Because of cardiomyopathy associated with dystrophinopathies, we did not observe *de novo* heart failure. Also, we did not observe AHF with hypertensive setting. Indeed, most of the patients were already treated with angiotensin-converting enzyme inhibitors and beta-blockers and in practice tended to have hypotension. In our study, patients ventilated with duration of 24 h/24 h disclosed mainly right signs of AHF. Conversely, patients with intermittent HMV experienced dyspnoea related to high left ventricular filling as AHF clinical presentation.

As a consequence of limited mobility, symptoms are often absent in DMD patients with stable cardiomyopathy. In the study by Nigro *et al.*,¹² only 28% of patients aged <18 years disclosed symptoms. In adult DMD patients with permanent mechanical ventilation, peripheral oedema, and ascites are classical and are associated with pleural effusion mainly in end-stage disease.¹⁰ The predominant right signs and peripheral oedema in patients with chronic mechanical ventilation are explained by the positive intra-thoracic

pressures that impede the venous return,¹⁰ and by the impact of mechanical ventilation on haemodynamic. Mechanical ventilation increases intra-thoracic pressure leading to a decrease of the venous return and an increase of the caval vein pressure,¹³ which corresponds to a decrease of the preload of the right ventricle. In the meantime, the positive intra-thoracic pressure increases the after load of the right ventricle, resulting in a global adverse effect on the right heart. On the left heart side, mechanical ventilation has a favourable effect on the heart performance, decreasing the transmural pressure of the left ventricle and thus the after load.

Prognosis of AHF episodes depends on degree of congestion (wet or dry) and adequacy of perfusion (warm or cold).¹⁴ In our study, intra-hospital global mortality rate in patients admitted for AHF was 30% in the whole studied population, reaching 53.8% after 1 year. Mortality rate was high in the subgroup of patients with previous admission for AHF and those with cardiogenic shock on admission. Indeed, cardiogenic shock¹⁵ is associated with 16.8% mortality in the general cardiologic population, according to the OFICA study.¹⁶ Left ventricular EF has been reported to be a predictive factor for mortality in DMD.¹⁷ Also, LBBB is associated with heart failure and poor prognosis.¹⁸ The mortality we observed in our population lies well higher than that of the general cardiologic population. This could be due to some particularities of the DMD-associated end stage cardiomyopathy (mean left ventricular EF at 25% in our study). The majority of patients was invasively ventilated and had severe motor impairment and morbidity. In DMD, adult patients disclose a severe dilated cardiomyopathy with fibrosis. The mortality rate in ICU is notably high in this situation, and cardiac resynchronization therapy has been used as an invasive electronic treatment for rescue therapy in some selected patients with severe heart failure and complete LBBB.¹⁹

Adult patients with DMD are at high risk of AHF because of cardiomyopathy due to the lack of dystrophin.²⁰ Dystrophin has four main regions: an N-terminal actin-binding domain, a central rod domain formed by 24 spectrin-like repeats and four hinges, a cysteine-rich domain, and a carboxy-terminal domain.²¹ Dystrophin acts as a scaffolding protein for other proteins and protects sarcolemma from contraction muscle stress.⁵ The lack of dystrophin leads to progressive fibre damage and membrane leakage, resulting in a progressive muscle wasting and weakness of variable distribution and severity.^{20,22} Genotype-phenotype correlation is challenging in dystrophinopathies. Deletions in the hotspot region (exons 45–55) seem to be associated with a milder disease picture.²³ Kaspar *et al.*²⁴ reported dilated cardiomyopathy particularly in BMD with mutations affecting exons 2–9, corresponding to the actin-binding amino-terminal of dystrophin. In dystrophinopathies patients, Jefferies *et al.*²⁵ reported heart involvement mainly in patients with mutation located from exon 12 to exon 17. As

a more general rule, it has been demonstrated that cardiomyopathy severity in BMD patients is linked to the structure of dystrophin.²⁶ In our study, we did not find a significant relationship between genetic and clinical patterns. The absence of positive correlation between genetic pattern and clinical phenotype in our study may be explained by the small number of patients and the fact that all mutations are truncated leading to absence of dystrophin. However, the fact that all of the 13 patients that fulfilled our inclusion criteria harboured *DMD* mutations involving at least the N-terminal and rod domains may suggest that involvements of these two domains had a higher deleterious effect on cardiac function.

Renal failure is a classical complication in cardiogenic shock. The GFR (glomerular filtration rate) is often reduced in patients with advanced chronic heart failure and renal function is a powerful independent predictor of prognosis in heart failure.²⁷ In DMD, because of muscle loss and impairment, it is difficult to assess renal injury level using only creatinine level dosage in blood. In our study, blood creatinine levels >20 $\mu\text{mol/L}$ were found in 46% of patients with AHF. It is possible that a number of patients develop cardio-renal syndrome despite a 'normal' creatinine level in blood. Serum cystatin C could be more appropriate to assess acute renal injury.²⁸

Finally, the higher intra-hospital and 1 year mortality of adult DMD patients with cardiogenic shock complicating end stage cardiomyopathy raises ethical questions regarding the place for potential left ventricle assist device (LVAD). However, in the general population, LVAD implantation exposes the patient to complications that include thrombo-embolic events, stroke, bleeding, and sepsis and right ventricular failure. We also know that DMD patients disclose a specific pattern that include respiratory restrictive pattern (rib cage stiffness, kyphoscoliosis, and thoracic reduced compliance),⁷ digestive impairment (gastric dilatation and risk of pseudo intestinal obstruction), osteoporosis, fragile tissue in relation with steroid long-term treatment, small body surface area, and denutrition. An Italian group reported recently data about LVAD as destination therapy in young DMD patients.²⁹ However, morbidity and mortality remain higher because of per-operative and post-operative complications.²⁹ Thus, in the light of our results, we recommend that such a procedure should be discussed within interdisciplinary heart failure teams specialized in the management of severe DMD with end-terminal heart failure in connection with caring physicians and patient family.

The main strength of our study consists in its original approach in this group of neuromuscular disease and the description of genetic and cardiac patterns and prognosis.

We acknowledge limitations regarding our results. Although relying on the long-term experience of a reference centre for neuromuscular disease, the number of described patients remains rather small, limiting the power of statistical

comparisons, and our study is retrospective. The recruitment of our centre is another bias. In fact, the patients admitted in ICU are particularly severe with baseline tracheotomy, gastrostomy, and severe heart failure.

Conclusions

AHF is a life-threatening complication in DMD, but its recognition may be difficult, because clinical presentation may be atypical and often limited to anasarca or right cardiac

failure signs. In DMD and BMD patients with severe left ventricular dysfunction admitted to the ICU for AHF, the intra-hospital mortality rate was 30%, and the 1 year mortality 53%. In case of cardiogenic shock, intra-hospital mortality rate was notably high (66%), reaching 83.3% at 1 year.

Conflict of interest

None declared.

References

- Hoffman EP, Fischbeck KH, Brown RH, Johnson M, Medori R, Loike JD, Harris JB, Waterston R, Brooke M, Specht L et al. Characterization of dystrophin in muscle-biopsy specimens from patients with Duchenne's or Becker's muscular dystrophy. *N Engl J Med* 1988; **318**: 1363–1368.
- Monaco AP, Bertelson CJ, Liechti-Gallati S, Moser H, Kunkel LM. An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. *Genomics* 1988; **2**: 90–95.
- Koenig M, Beggs AH, Moyer M, Scherpf S, Heindrich K, Bettecken T, Meng G, Müller CR, Lindlöf M, Kaariainen H, de la Chapelle A, Kiuru A, Savontaus ML, Gilgenkrantz H, Récan D, Chelly J, Kaplan JC, Covone AE, Archidiacono N, Romeo G, Liechti-Gallati S, Schneider V, Braga S, Moser H, Darras BT, Murphy P, Francke U, Chen JD, Morgan G, Denton M, Greenberg CR, Wrogemann K, Blonden LA, van Paassen MB, van Ommen GJ, Kunkel LM. The molecular basis for Duchenne versus Becker muscular dystrophy: correlation of severity with type of deletion. *Am J Hum Genet* 1989; **45**: 498–506.
- Stearse SE, Dubowitz V, Benatar A. Subclinical cardiomyopathy in Becker muscular dystrophy. *Br Heart J* 1992; **68**: 304–308.
- Petrof BJ, Shrager JB, Stedman HH, Kelly AM, Sweeney HL. Dystrophin protects the sarcolemma from stresses developed during muscle contraction. *Proc Natl Acad Sci U S A* 1993; **90**: 3710–3714.
- Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscul Disord* 2002; **12**: 926–929.
- Simonds AK, Muntoni F, Heather S, Fielding S. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax* 1998; **53**: 949–952.
- Gheorghiadu M, Zannad F, Sopko G, Klein L, Piña IL, Konstam MA, Massie BM, Roland E, Targum S, Collins SP, Filippatos G, Tavazzi L, International Working Group on Acute Heart Failure Syndromes. Acute heart failure syndromes: current state and framework for future research. *Circulation* 2005; **112**: 3958–3968.
- Deburgrave N, Daoud F, Llense S, Barbot JC, Récan D, Peccate C, Burghes AH, Bérout C, Garcia L, Kaplan JC, Chelly J, Leturcq F. Protein- and mRNA-based phenotype-genotype correlations in DMD/BMD with point mutations and molecular basis for BMD with nonsense and frameshift mutations in the DMD gene. *Hum Mutat* 2007; **28**: 183–195.
- Faysoil A, Ritzenthaler T, Luis D, Hullin T, Clair B, Annane D, Orlikowski D. Be careful about abdominal discomfort in adult patients with muscular dystrophy. *Rev Neurol (Paris)* 2014; **170**: 548–550.
- Jardin F, Farcot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP. Influence of positive end-expiratory pressure on left ventricular performance. *N Engl J Med* 1981; **304**: 387–392.
- Nigro G, Comi LI, Politano L, Bain RJ. The incidence and evolution of cardiomyopathy in Duchenne muscular dystrophy. *Int J Cardiol* 1990; **26**: 271–277.
- Smeding L, Lust E, Plötz FB, Groeneveld AB. Clinical implications of heart–lung interactions. *Neth J Med* 2010; **68**: 56–61.
- Thomas SS, Nohria A. Hemodynamic classifications of acute heart failure and their clinical application:—an update. *Circ J* 2012; **76**: 278–286.
- Topalian S, Ginsberg F, Parrillo JE. Cardiogenic shock. *Crit Care Med* 2008; **36**: S66–S74.
- Logeart D, Isnard R, Resche-Rigon M, Seronde MF, de Groot G, Jondeau G, Galinier M, Mulak G, Donal E, Delahaye F, Juilliere Y, Damy T, Jourdain P, Bauer F, Eicher JC, Neuder Y, Trochu JN, Heart Failure of the French Society of Cardiology. Current aspects of the spectrum of acute heart failure syndromes in a real-life setting: the OFICAs study. *Eur J Heart Fail* 2013; **15**: 465–476.
- Corrado G, Lissoni A, Beretta S, Terenghi L, Tadeo G, Foglia-Manzillo G, Tagliagambe LM, Spata M, Santarone M. Prognostic value of electrocardiograms, ventricular late potentials, ventricular arrhythmias, and left ventricular systolic dysfunction in patients with Duchenne muscular dystrophy. *Am J Cardiol* 2002; **89**: 838–841.
- Calvert LD, McKeever TM, Kinnear WJ, Britton JR. Trends in survival from muscular dystrophy in England and Wales and impact on respiratory services. *Respir Med* 2006; **100**: 1058–1063.
- Faysoil A, Nardi O, Annane D, Orlikowski D. Successful cardiac resynchronisation therapy in Duchenne muscular dystrophy: a 5-year follow-up. *Presse Med* 2014; **43**: 330–331.
- Spurney CF. Cardiomyopathy of Duchenne muscular dystrophy: current understanding and future directions. *Muscle Nerve* 2011; **44**: 8–19.
- Le Rumeur E, Winder SJ, Hubert JF. Dystrophin: more than just the sum of its parts. *Biochim Biophys Acta* 2010; **1804**: 1713–1722.
- Muntoni F, Torelli S, Ferlini A. Dystrophin and mutations: one gene, several proteins, multiple phenotypes. *Lancet Neurol* 2003; **2**: 731–740.
- Aartsma-Rus A, Ginjaar IB, Bushby K. The importance of genetic diagnosis for Duchenne muscular dystrophy. *J Med Genet* 2016; **53**: 145–151.
- Kaspar RW, Allen HD, Ray WC, Alvarez CE, Kissel JT, Pestronk A, Weiss RB, Flanigan KM, Mendell JR, Montanaro F. Analysis of dystrophin deletion mutations predicts age of cardiomyopathy onset in Becker muscular dystrophy. *Circ Cardiovasc Genet* 2009; **2**: 544–551.
- Jefferies JL, Eidem BW, Belmont JW, Craigen WJ, Ware SM, Fernbach SD,

- Neish SR, Smith EO, Towbin JA. Genetic predictors and remodeling of dilated cardiomyopathy in muscular dystrophy. *Circulation* 2005; **112**: 2799–2780.
26. Nicolas A, Raguénès-Nicol C, Ben Yaou R, Ameziane-Le Hir S, Chéron A, Vié V, Claustres M, Leturcq F, Delalande O, Hubert JF, Tuffery-Giraud S, Giudice E, Le Rumeur E, French Network of Clinical Reference Centres for Neuromuscular Diseases (CORNEMUS). Becker muscular dystrophy severity is linked to the structure of dystrophin. *Hum Mol Genet* 2015; **24**: 1267–1279.
27. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members, Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**: 891–975.
28. Villa CR, Kaddourah A, Mathew J, Ryan TD, Wong BL, Goldstein SL, Jefferies JL. Identifying evidence of cardio-renal syndrome in patients with Duchenne muscular dystrophy using cystatin C. *Neuromuscul Disord* 2016; **26**: 637–642.
29. Perri G, Filippelli S, Adorisio R, Iacobelli R, Iodice F, Testa G, Paglietti MG, D'Amario D, Massetti M, Amodeo A. Left ventricular assist device as destination therapy in cardiac end-stage dystrophinopathies: midterm results. *J Thorac Cardiovasc Surg* 2017; **153**: 669–674.